

REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the following remarks.

Amendments to the claims were made for purposes of clarifying the structure of the claimed composite liposome. Independent claim 18 has been so amended. Support for the amendments to the claims can be found throughout the application as filed. No new matter has been added by the amendments to the specification or the claims.

1. Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner takes the position that, "Claim 18 is confusing. What is it applicant is claiming? A composite liposome which has a invaginated vase-like structure or which will form the invaginated vase-like structure. If it is the latter, then how does the vase-like structure form? The step involved should be recited. It is also unclear as recited, whether two separate bilayer structures are involved or one liposome with two bilayers and the active agent is outside the top bilayer. Clarification is requested.".

Applicants have amended independent claim 18 for the purpose of clarifying the claim language such that the subject matter claimed clearly relates to composite liposomes having an invaginated vase-like structure.

2. Claims 18-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,413,544 ('544 patent).

The Examiner takes the position that, "Although the conflicting claims are not identical, they are not patentably distinct from each other because instant generic 'liposome' and 'sandwich liposome' encompass the

specific 'sandwich liposome' recited in claims 1 and 2 of said patent. Instant process of preparation which is the same as the patented process (claim 3), but drawn to generic 'biologically active agent' encompasses the DNA in the patented claim.

Applicants are concurrently filing herewith a Terminal Disclaimer which disclaims, with regard to claims Claims 18-19 of the 10/825,803 application, the terminal portion of any patent granted on this application which would extend beyond the expiration of the '544 patent. As such, the basis for this rejection is obviated.

3. Claims 18-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,770,291 ('291 patent).

The Examiner takes the position that, "Although the conflicting claims are not identical, they are not patentably distinct from each other because instant generic 'liposome' and 'sandwich liposome' encompass the specific 'sandwich liposome' recited in claims 1 and 2 of said patent. Instant process of preparation which is the same as the patented process (claim 3), but drawn to generic 'biologically active agent' encompasses the DNA in the patented claim.".

Applicants are concurrently filing herewith a Terminal Disclaimer which disclaims, with regard to claims Claims 18-19 of the 10/825,803 application, the terminal portion of any patent granted on this application which would extend beyond the expiration of the '291 patent. As such, the basis for this rejection is obviated.

4. Claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by WO93/25673 of record.

The Examiner takes the position that, "WO discloses liposomes made of DOTAP, cholesterol derivative and DNA (note the abstract, Examples, example 2 in particular). The liposomes can be targeted (page 29). Since WO discloses liposomes containing the same components and prepared by sonication, the burden is upon applicant to show that the prior art liposomes are different from instant liposomes.".

Applicants respectfully disagree with the Examiner's assertions. It should be noted that the claims of the present application relate to liposomes which have an invaginated vase-like structure, which is principally due to the novel method of preparing the liposomes of the present invention. These invaginated vase-like structure liposomes offer significant advantages, particularly with regard to efficiency of delivery. WO93/25673 makes no reference to liposomes having an invaginated vase-like structure. Furthermore, the method of preparing liposomes mentioned in Example 2 is quite different from the present invention. In Example 2 of WO93/25673, the lipids and cholesterol are mixed together, evaporated to dryness, resuspended by vortexing and sonicated. The methods of the present invention involve heating a mixture of lipids and cholesterol, sonicating the mixture and then extruding the lipid components sequentially through filters of decreasing pore size which forms the invaginated liposomes.

5. Claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Parks (5,230,899).

The Examiner takes the position that, "Claim 18 can be interpreted as a liposome having a bilayer within a bilayer and the presence of the biologically active agent present outside and inside since forming an invaginated vase like structure is an intended function. In essence, this reads on a multilamellar liposomes having a hydrophilic agent which is inside and outside the liposomes.

Park discloses multilamellar liposomes containing arginine (biologically active agent) (abstract, col. 4, lines 46-60, Examples, example 2 in particular and claims). Since the claim recites the intended function, the burden is shifted to applicant to show that Park's liposomes do not form the same claimed structure.".

Applicants respectfully disagree with the Examiner's assertion. The subject matter disclosed and claimed in the '899 patent relates to liposomes made with hydrating agents. In fact, the '899 patent teaches away from the use of sonication as a means of forming liposomes. For example, in column 3, lines 18-25 state, "Liposomes made with hydrating agents are more stable than the ones produced by conventional methods, including those formed using organic solvents and ultrasonic energy. Liposome formulations having these hydrating agents suffer none of the solvent removal problems of the current

technology nor are the liposomes beset by the non-uniform, destructive forces of ultrasonic irradiation inherent in the older methods.". As such, the liposomes of the present application are not anticipated by the teachings of the '899 patent.

6. Claims 18-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Debs (5,827,703).

The Examiner takes the position that, "Debs discloses liposomes containing DOTAP, Cholesterol derivative and DNA (note the abstract and Example 2 on columns 19-20. Since Debs discloses liposomes containing the same components and prepared by sonication, the burden is upon applicant to show that the prior art liposomes are different from instant liposomes.".

Applicants respectfully disagree with the Examiner's assertion. The same argument recited above with regard to WO93/25673 is applicable for Debs, as well since the liposomes of Debs are prepared by the same method used in Wo93/25673. The '703 patent makes no reference to liposomes having an invaginated vase-like structure. Furthermore, the method of preparing liposomes mentioned in Example 2 is quite different from the present invention. In Example 2 of '703, the lipids and cholesterol are mixed together, evaporated to dryness, resuspended by vortexing and sonicated. The methods of the present invention involve heating a mixture of lipids and cholesterol, sonicating the mixture and then extruding the lipid components sequentially through filters of decreasing pore size which forms the invaginated liposomes.

7. 18-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Feigner (5,580,859).

The Examiner takes the position that, "Feigner discloses instant liposomes, liposomes contain DOTAP, cholesterol and nucleic acids (note col. 26, line 51 and example 6). Since Feigner discloses liposomes containing the same components and prepared by sonication, the burden is upon applicant to show that the prior art liposomes are different from instant liposomes.".

Applicants respectfully disagree with the Examiner's assertion. Once again, the method of preparing liposomes in the '859 patent is quite different than the method of the present invention, even though they both may involve sonication. Given the significant differences, the method of preparing liposomes in the '859 patent would not result in producing liposomes with invaginated vase-like structures.

For each and all of the foregoing reasons and in view of the foregoing amendment, it is believed that Claims 18 and 19 as hereinabove amended now are in condition for allowance. Favorable reconsideration and allowance of this application, therefore, is respectfully requested in response to this communication.

Applicants believe that additional fees are not required to complete the filing requirements for the subject application or otherwise in connection with this submission. However, if a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge/credit Deposit Account No. **04-1105**.

Respectfully submitted,

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